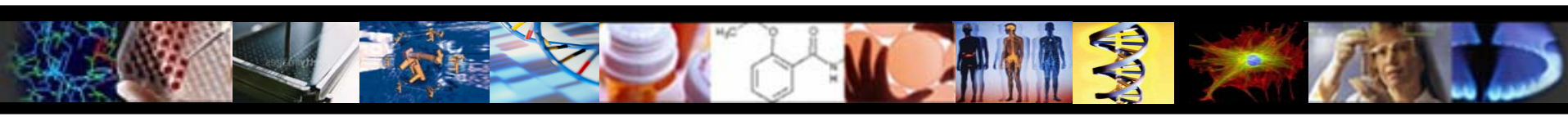
Advisory Committee to the NIH Director

Proposed NIH Policy for Data Sharing of NIH-Supported Genome-Wide Association Studies (GWAS)



Elizabeth G. Nabel, M.D.
Director
National Heart, Lung, and Blood Institute

James Ostell, Ph.D.
Chief, Information Engineering Branch
NCBI, National Library of Medicine

December 1, 2006

National Heart Lung and Blood Institute
People Science Health

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What are GWAS?

A genome-wide association study (GWAS) is defined as a study of genetic variation across the human genome, which is designed to identify genetic associations with observable traits, such as blood pressure or weight, or the presence or absence of a disease or condition.

Guiding Principle:

The greatest public benefit will be realized if data from GWAS are made available, under terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of investigators.

Rationale: Data Sharing

- **NIH is the steward of the American public's investment in global health.**
- **Information which is not shared represents lost opportunity to improve the health of the public.**
- **NIH has been encouraging wide sharing of information for several years.**

Proposed NIH Policy for GWAS

- **Data Management**
  - **Protection of Research Participants**
  - **Data Submission Procedures**
  - **Data Access Principles**
- **Scientific Publication**
- **Intellectual Property**

GWAS Data Management Overview

Data Collection

Submission & Management of Data

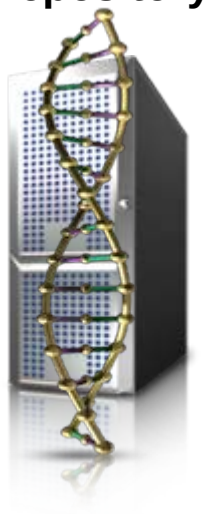
Research Participants

Informed consent

Submitting Investigators

Identifying information removed, replaced with random unique code

GWAS data repository



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Human Subjects Issues – Data Submission

- **Local IRB approval required prior to submission to GWAS data repository**
- **Submission accompanied by institutional statement that data is provided in accord with all applicable laws and regulations**
- **Information regarding any limitations on data use is requested at time of application (e.g., limitations imposed by existing informed consent)**
- **The GWAS Database itself would not be engaging in human subjects research**
  - **Data will be coded by submitting investigators**
  - **Agreements will be signed stipulating that key codes will not be shared**

Potential Identifiers

- **Geographic subdivisions smaller than the state will be needed for genetic-environmental interaction studies**
- **Dates smaller than a year may be needed for some studies**
- **A code will be retained to link to data so that it can be updated or withdrawn**

GWAS Data Management Overview

Data Collection → Submission & Management of Data → Distribution & Secondary Use of Data

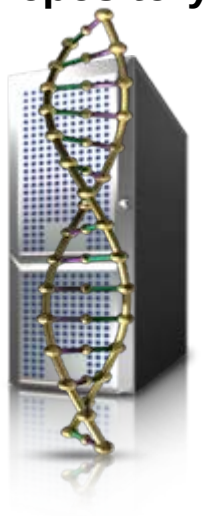
Research Participants

Informed consent

Submitting Investigators

Identifying information removed, replaced with random unique code

GWAS data repository



Data Access Request for Coded data

Recipient Investigators

National Heart Lung and Blood Institute
People Science Health

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Data Access Committee

- **Model Data Access Committees Policies and Procedures have been developed by GAIN and Framingham SHARe and GAIN.**
- **Investigators who request GWAS data provide through a Data Distribution Agreement**
  - **Description of proposed research projects**
  - **Data Use Certification agreeing to defined period during which manuscripts will not be submitted for publication**
  - **Agreement to protect confidentiality of data**
  - **Annual progress reports**

Human Subjects Issues – Data Access

- **OHRP has confirmed that secondary data users will not be conducting human subjects research under 45 CFR 46**
- **Access requests may ask for proposed research use of data**
  - **Specified research use parameters should respect original informed consent provisions**
- **Access requests will stipulate that requestors will NOT:**
  - **Attempt to identify individuals within the study**
  - **Share the data with third parties**
- **Investigators and home institutions will be responsible for compliance with federal, state, and local policies, such as**
  - **HIPAA**
  - **45 CFR 46**
  - **Local institutional review**

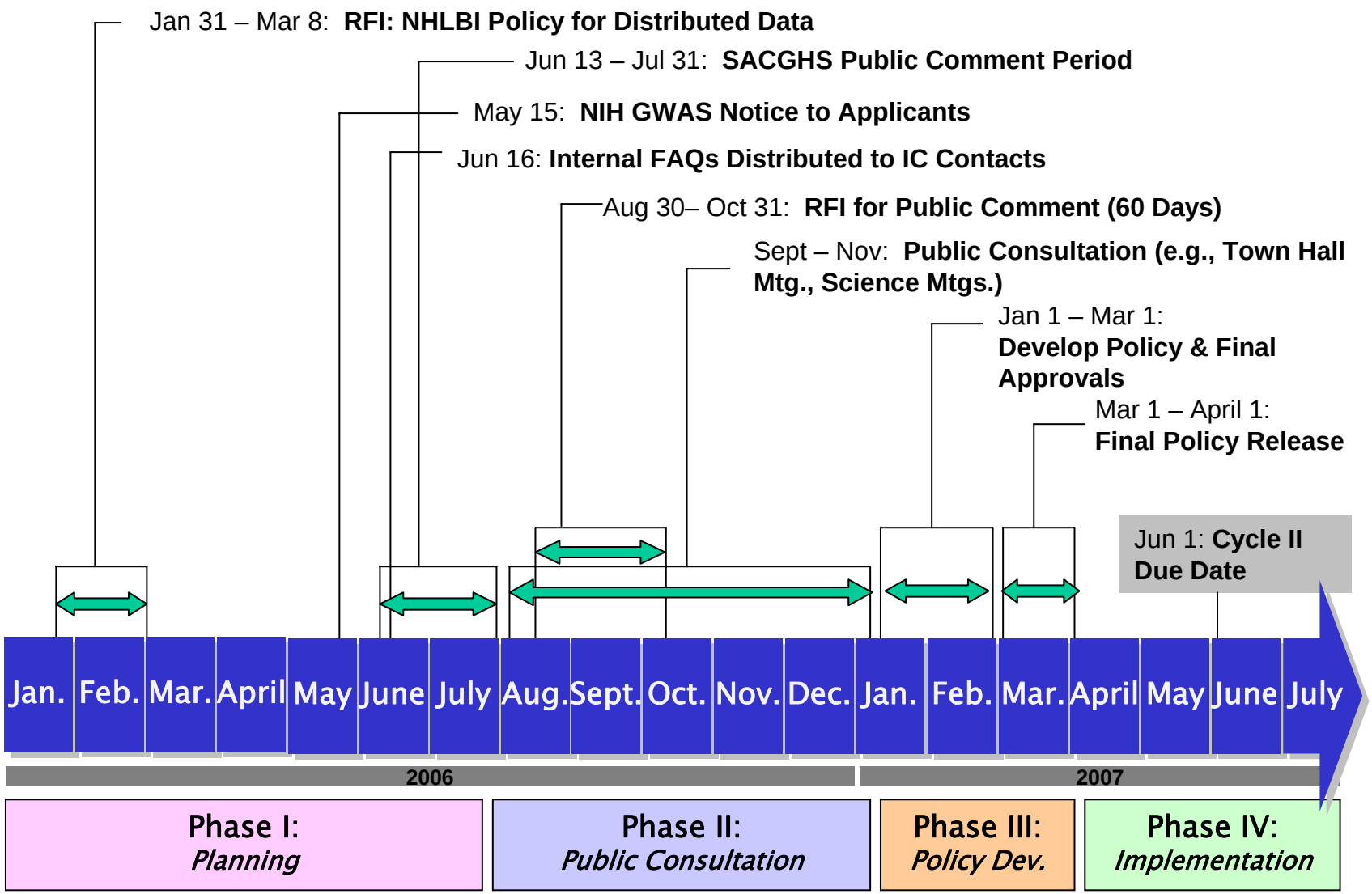
Publication

- **Period of exclusivity for Primary Investigators**
  - **Proposed period 9 months**
- **Acknowledgement of contributing investigators and funding organization**

Intellectual Property

- **NIH urges that genotype-phenotype associations remain available to all investigators, unencumbered by IP claims**
- **NIH discourages premature claims on pre-competitive information**
- **NIH encourages broad use of NIH supported genotype-phenotype data consistent with NIH's Best Practices for Licensing with Genomic Inventions**

Timeline for Proposed GWAS Policy



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Genome-Wide Association Studies (GWAS)

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About OER

The NIH is interested in advancing Genome-Wide Association Studies (GWAS) to identify common genetic factors that influence health and disease because the information derived from such studies will be essential for developing new approaches to reduce disease burden and promote health. GWAS are currently defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition. The goal of the proposed policy is to advance science for the benefit of the public through the creation of a centralized NIH GWAS data repository. The purpose of this Website is to support the public consultation process to inform policy development activities.

The "Overview" section of this site presents the essential background and responses to frequently asked questions. The items on this page focus on the notices released to date which will result in a request for information through which the National Institutes of Health seeks comments.

Overview

- Background

Notices and Announcements

- Submit a Comment - Comments were due by October 31, 2006.
- NIH Press Release (08/30/2006) - NIH Proposes Repository for Genetic Information
- Federal Register Notice (08/30/2006) - Request for Information (RFI): Proposed Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)
- NIH Guide Notice NOT-OD-06-094 (08/30/2006) - Request for Information (RFI): Proposed Policy for Sharing of Data obtained in NIH supported or conducted Genome-Wide Association Studies (GWAS)
- NIH Guide Notice NOT-OD-06-071 (05/15/2006) - Notice to Applicants for NIH Genome-Wide Association Studies

Comments or Questions?

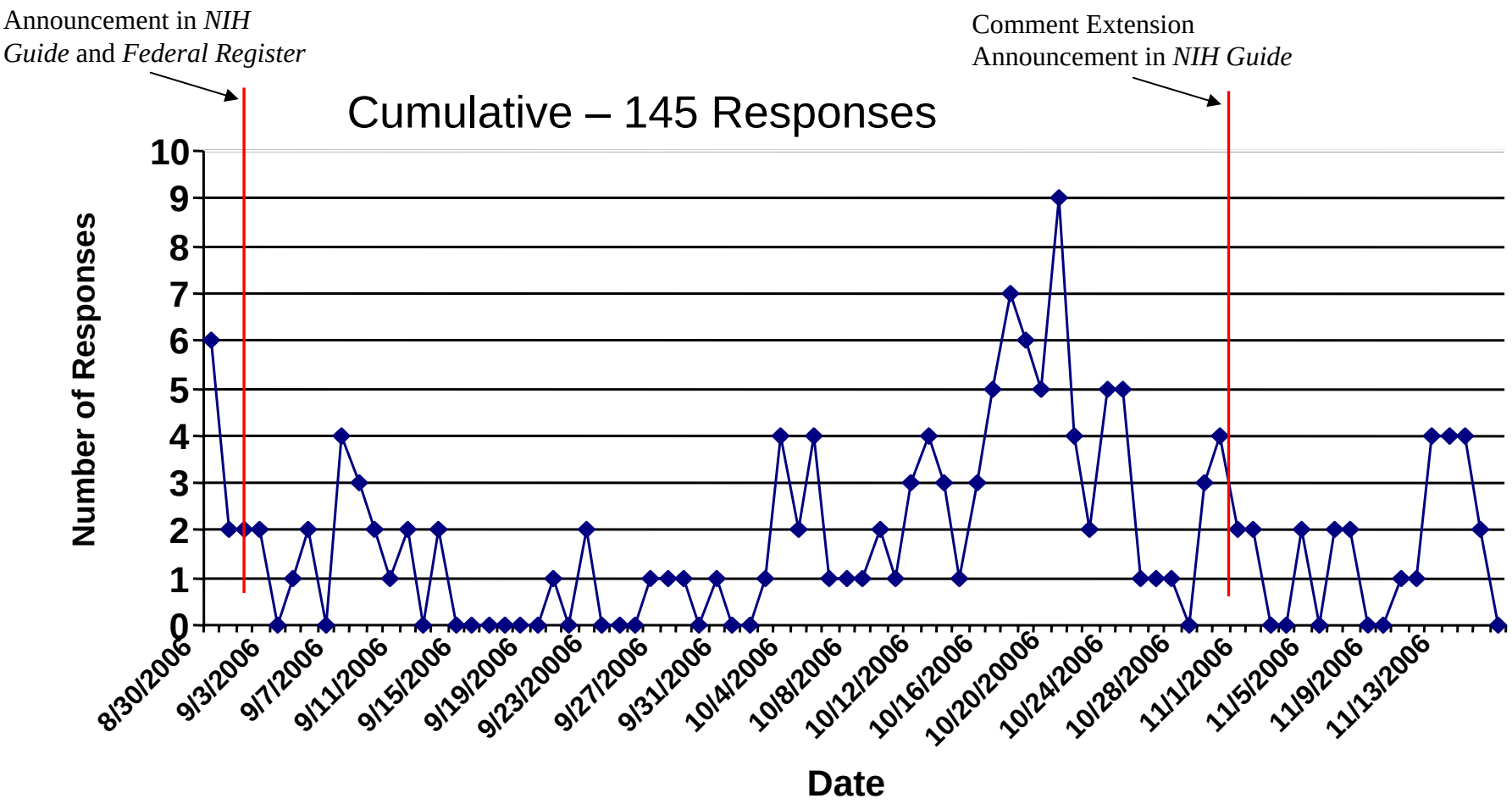
- Please send email to GWAS@nih.gov.

Google: "GWAS policy"

Questions for Public Consultation

1. What are potential benefits and risks to research participants of sharing phenotypic and genotypic data without information that would identify research participants?
2. Are additional protections needed to minimize risks to research participants whose personal identifying information has been removed?
3. What are the advantages and disadvantages of:
    a. A centralized NIH data repository?
    b. The proposed approach to data submission?
    c. A grace period for scientific publication?
    d. The approach to intellectual property?
4. What specific resources may investigators and institutions need to meet the goals of this proposed policy?

GWAS Number of Comments Received Daily August 30 – November 16, 2006



This represents all the comments received during the commenting period but we are still verifying through our quality control process that there are no duplicate records, and that all the responses mailed, e-mailed or faxed have been entered into the database.

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For More Information

- **http://grants.nih.gov/grants/gwas/index.htm**
- **GWAS@nih.gov**
- **Town Hall Meeting: December 14, 2006, Bethesda**

Benefits of the GWAS Data Repository

- **Improve Health:** Better understand the health needs of the public and facilitate the development of improved diagnostic tools and design of new, safe and highly effective treatments.
- **Maximize Public Investment:** Accelerate the discovery of associations between genetic data and disease, while minimizing research costs.

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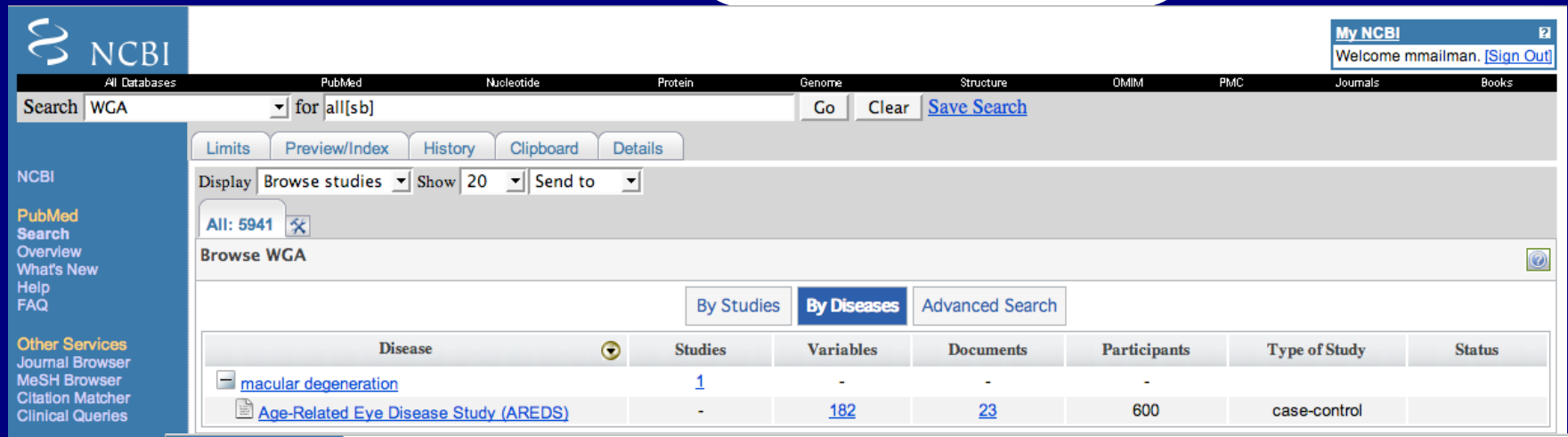
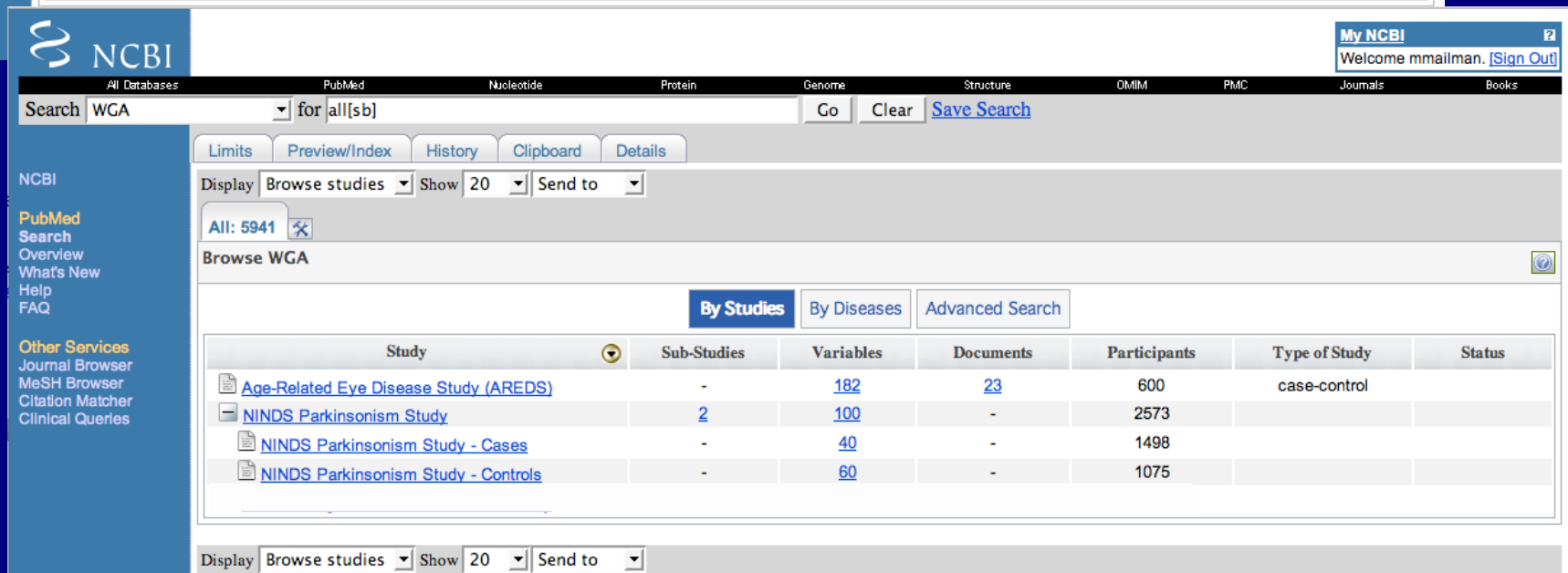
GENOTYPE and PHENOTYPE





NEI Age-Related Eye Disesase Study (AREDS), Version 1

ID: 1

NEI Age-Related Eye Disesase Study (AREDS)

Description

The Age-Related Eye Disease Study (AREDS) was initially conceived as a long-term multicenter, prospective study of the clinical course of age-related macular degeneration (AMD) and age-related cataract. In addition to collecting natural history data, AREDS included a clinical trial of high-dose vitamin and mineral supplements for AMD and a clinical trial of high-dose vitamin supplements for cataract. Results from these clinical trials have been published. The two clinical trials generally shared 1 pool of participants (Figure 1). The clinical trials were initiated largely because of the widespread public use in the United States of commercially available pharmacologic doses of vitamins and minerals to treat these two eye conditions and the absence of definitive studies on the safety and efficacy of their use.

Eligible AREDS participants were age 55 to 80 years of age at enrollment and had to be free of any illness or condition that would make long-term follow-up or compliance with study medications unlikely or difficult. On the basis of fundus photographs graded by a central reading center, best-corrected visual acuity and ophthalmologic evaluations, participants were enrolled in one of several AMD.

It is hoped that this resource will help researchers better understand two important diseases that affect an aging population. The AREDS Research Group hopes that data from AREDS on progression rates and risk factors for AMD and cataract will further understanding of the clinical course of both conditions, generate hypotheses about etiology and aid in the design of clinical trials of potential interventions.

- Subjects: 600
- Type: case-control
- Status:

History

AREDS Time Line

- November 1992 - first qualifying visit
- February 1993 - first randomization visit
- December 1993 - first annual visit
- February 1994 - release of Finnish study results
- December 1994 - second annual visits
- January 1996 - release of Caret study results
- March 1996 - implementation of sunlight exposure questionnaire (SEQ) and reassignment of smokers to non-antioxidant study medications
- April 1997 - implementation of visual function questionnaire with appendix (NEI VFQ)
- January 1998 - implementation of 5th year follow-up interview, approval of genetics ancillary study, and end of recruitment
- May 1998 - first blood drawn for genetics ancillary study
- June 2000 - implementation of cognitive function protocol; April 2001 - last phase II study visit
- Fall 2001 - trial results announced and initiation of phase III
- December 2005 - end of study

Links

- Age-Related Eye Disease Study Research Group
  The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1.
  Controlled clinical trials. 1999 Dec ; 20(6):573-600
- Age-Related Eye Disease Study Research Group
  The Age-Related Eye Disease Study: a clinical trial of zinc and antioxidants--Age-Related Eye Disease Study Report No. 2.
  The Journal of nutrition. 2000 May ; 130(5S Suppl):1516S-9S
- Age-Related Eye Disease Study Research Group
  Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3.
  Ophthalmology. 2000 Dec ; 107(12):2224-32
- Age-Related Eye Disease Study Research Group
  The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4.
  American journal of ophthalmology. 2001 Feb ; 131(2):167-75
- Age-Related Eye Disease Study Research Group
  Risk factors associated with age-related nuclear and cortical cataract : a case-control study in the Age-Related Eye Disease Study, AREDS Report No. 5.
  Ophthalmology. 2001 Aug ; 108(8):1400-8
- Age-Related Eye Disease Study Research Group
  The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6.
  American journal of ophthalmology. 2001 Nov ; 132(5):668-81
- Age-Related Eye Disease Study Research Group
  The effect of five-year zinc supplementation on serum zinc, serum cholesterol and hematocrit in persons randomly assigned to treatment group in the age-related eye disease study: AREDS Report No. 7.
  The Journal of nutrition. 2002 Apr ; 132(4):697-702
- Age-Related Eye Disease Study Research Group
  A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.
  Archives of ophthalmology. 2001 Oct ; 119(10):1417-36
- Age-Related Eye Disease Study Research Group
  A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9.
  Archives of ophthalmology. 2001 Oct ; 119(10):1439-52
- Clemons TE, Chew EY, Bressler SB, McBee W, Age-Related Eye Disease Study Research Group
  National Eye Institute Visual Function Questionnaire in the Age-Related Eye Disease Study (AREDS): AREDS Report No. 10.
  Archives of ophthalmology. 2003 Feb ; 121(2):211-7
- Bressler NM, Bressler SB, Congdon NG, Ferris FL, Friedman DS, Klein R, Lindblad AS, Milton RC, Seddon JM, Age-Related Eye Disease Study Research Group
  Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11.
  Archives of ophthalmology. 2003 Nov ; 121(11):1621-4
- Yaffe K, Clemons TE, McBee WL, Lindblad AS, Age-Related Eye Disease Study Research Group
  Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial.
  Neurology. 2004 Nov ; 63(9):1705-7

Search Within This Study

Search for: Go

Variables

smk09
smk10
smk11
smk12
smk13
syst00
syst03
syst04
syst05
syst06
syst07
syst08
syst09
syst10
syst11
syst12
syst13
dias00

Documents

- Chapter 1: Background and rationale
- Chapter 2: Literature review
- Chapter 3: Study design
- Chapter 4: Study rationalization
- Chapter 10: Description of intervention
- Chapter 5: Study policies
- Chapter 11: Data analysis and reporting
- Baseline interview — phase II
- Chapter 6: Examination schedule
- Chapter 12: Quality enhancement
- Sunlight exposure questionnaire — phase II
- Chapter 7: Examination procedures
- Chapter 13: Clinical center procedures
- Missed visit — phase II
- Chapter 8: Photographic procedures
- Chapter 14: Coordinating center procedures

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on-antioxidant study medications

nd of recruitment

Report No. 2.

disease study: Age-Related Eye Disease Study Report Number 3.

rt no. 4.

ed Eye Disease Study, AREDS Report No. 5.

pic color fundus photographs: the Age-Related Eye Disease Study

ndomly assigned to treatment group in the age-related eye disease

rotene, and zinc for age-related macular degeneration and vision loss:

a carotene for age-related cataract and vision loss: AREDS report no. 9.

S Report No. 10.

Age-Related Eye Disease Study Research Group

Search Within This Study

Search for: Go

Variables

smk09
smk10
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syst00
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dias00

Documents

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- Missed visit — phase II
- Chapter 8: Photographic procedures
- Chapter 14: Coordinating center procedures

AREDS: Age Related Eye Disease Study

Chapter 7 EXAMINATION PROCEDURES

7.1 INTRODUCTION

The procedures for carrying out the examinations required in the study are described in this chapter. Required ocular examinations include refraction and visual acuity measurements, intraocular pressure measurement, and ophthalmoscopic examination. General characteristic assessments include measurement of height, weight, and blood pressure and determination of past medical history. Risk factor assessments will require the administration of the food frequency and sunlight exposure questionnaires as well as collection of blood specimens. Procedures for participant identification, masking, distribution and management of the supplementation, adherence assessment, and home visit examination are also described. Procedures for taking photographs of the lens and fundus are described in detail in Chapter 8. The schedule and description of participant visits in Chapter 6 outline the examinations required during each visit.

7.2 REFRACTION AND VISUAL ACUITY

A manifest refraction and visual acuity measurement according to the detailed study protocol must be performed during (a) the Qualifying Visit when the visual acuity score using Chart R is 73 letters or less in at least one eye, (b) the Randomization Visit, (c) Annual Visits, and (d) any Nonannual Visit when the visual acuity score using Chart R has dropped by 10 letters or more compared to the Randomization Visit score for the first time. Participants' pupils should not be dilated at the time of visual acuity testing at any study visit; except they may be dilated during the Qualifying Visit. Pinhole acuity will not be tested as part of AREDS. At the Qualifying Visit, visual acuity may be initially assessed utilizing the participant's current distance glasses. At the Nonannual Visits, visual acuity is initially assessed utilizing the previously obtained manifest refraction. Participants will be asked to read the letters on Chart R only (not Charts 1 or 2), using the equipment described in Section 7.2.1. They will start reading from the top left-most letters--first with the right eye and then with the left eye. A visual acuity score will be calculated as described in Section 7.2.3.3. If at the Qualifying Visit the visual acuity is 74 letters or more in each eye or if at a Nonannual Visit the visual acuity is within nine letters of the Randomization Visit score in each eye, or a vision drop has already been documented in each eye, the visual acuities measured will be entered on the study form. For these participants, a manifest refraction and measurement of best-corrected visual acuity, using the detailed protocol (Sections 7.2.1 - 7.2.3), will not be required.

7.2.1 Visual Acuity Equipment and Facilities

7.2.1.1 Introduction.—The visual acuity of participants will be measured according to the standard procedure developed for the Early Treatment diabetic Retinopathy Study (ETDRS) and adapted for AREDS. The procedure is described in this section. The following equipment is used in AREDS: a set of three Lighthouse Distance Visual Acuity Test charts (second edition), which are modified ETDRS Charts 1, 2, and R, 1 and a retroilluminated box providing standardized chart illumination, as modified from the design by Ferris and Sperduto. 2 The charts and boxes are manufactured by:

Lighthouse Low Vision Products

36-02 Northern Boulevard

Long Island, New York 11101

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dbGaP

syst00
Version 1
ID: 94

NEI Age-Related Eye Disease Study (AREDS) >> syst00

Description

Sitting systolic blood pressure (at follow-up year 0)

Summary

Overall Summary Over All Subjects

Case vs. Control Distribution

Number of cases: 356
Number of controls: 172

Comparison of Values between Cases and Controls

"P = 0.04254Â (T-test)"

	All	Case	Control
Statistical Summary			
Mean:	136.3	137.5	134
Median:	134	134	132
Min:	74	74	96
Max:	204	204	180
N:	528	356	172
Null/Missing Values:	0	0	0
Invalid Values:	72	44	28
Standard Deviation:	18.6	19.11	17.29
Example Values (Count)			
	"130" (43)	"130" (34)	"150" (15)
	"120" (32)	"120" (26)	"140" (13)
	"150" (29)	"134" (17)	"138" (10)
	"140" (25)	"128" (15)	"124" (9)
	"124" (24)	"160" (15)	"130" (9)
	"132" (24)	"132" (15)	"132" (9)
	"128" (22)	"124" (15)	"122" (9)
	"138" (22)	"150" (14)	"136" (7)
	"160" (20)	"140" (12)	"128" (7)
	"134" (18)	"142" (12)	"118" (6)
Invalid Values (Count)			
	"." (72)	"." (44)	"." (28)

Related Documents

- Chapter 7: Examination procedures
- Baseline interview — phase II

Document Parts Related to Variable

- **Document Name:** Chapter 7: Examination procedures
  - See document part in context

7.6. BLOOD PRESSURE MEASUREMENT

Blood pressure measurements will be taken by a certified examiner using a standard mercury sphygmomanometer. Instructions for preparing the participant, using the proper techniques, utilizing equipment, and measuring and recording the blood pressure are provided below. Some institutions have installed electronic automated sphygmomanometers. In the interest of data consistency, standard mercury units are the instruments of choice; however it is recognized

- **Document Name:** Baseline interview — phase II
  - See document part in context

a.. Systolic (mmHg)

21 a..
ANTACIDS (eg, Tums, Rolaids, Mylanta): For how many years, over your lifetime, have you ta
least 5 times a week for more than 3 months?

- ○ Do not take it
- ○ < 5 years
- ○ ≥ 5 and < 10 years
- ○ ≥ 10 and < 20 years
- ○ ≥ 20 years

b.. Are you currently taking antacids regularly?

- ○ no
- ○ yes

I would like to take your blood pressure again, and then measure your height and weight.

22.. Sitting blood pressure (second reading). **(Participant must have been seated and quiet for measurement. See Section 7.6 of the Manual of Operations.):**

a.. Systolic **(mmHg)** [ ]
a.. Diastolic **(mmHg)** [ ]
b.. Certification number of blood pressure examiner: [ ]

23..

a.. Height **(to nearest inch):** [ ]
b.. Weight **(to nearet pound):** [ ]
c.. Certification number of height and weight examiner: [ ]

24.. Approximately how much did you weigh when you were 20 years of age? (lbs.) [ ]

25..

a.. Hematocrit **(%):** [ ]
b.. Method of hematocrit measurement:

- ○ Macro
- ○ Micro
- ○ Automated

c.. Date of blood draw: [ ]

For MALE participants, end of interview. Thank the participant, sign the form, and comp and date of interview on page 7.

For FEMALE participants, interview continues below.

WOMEN ONLY

I would like to ask you a few questions about your reproductive history.

26..
Have you ever been pregnant? **If no, skip to 27**

- Slide bottom weight balance (100 lb) first to participant's estimated gross weight; make sure that the weight balance is locked into its slotted position.
- Slide the top arm weight balance into position so that the scale indicator is centered.
- Carefully read measurement to the nearest 1 lb (tick mark).
- Say measurement aloud.
- Record measurement in pounds (lb) on form, filling in any leading zero.
- Ask participant to step down and recover his or her shoes and any clothes.

7.6. BLOOD PRESSURE MEASUREMENT

Blood pressure measurements will be taken by a certified examiner using a standard mercury sphygmomanometer. Instructions for preparing the participant, using the proper techniques, utilizing equipment, and measuring and recording the blood pressure are provided below. Some institutions have installed electronic automated sphygmomanometers. In the interest of data consistency, standard mercury units are the instruments of choice; however it is recognized that staff at those centers may have no alternative.

7.6.1. Participant Preparation

- The participant should be seated with feet flat and on the floor and legs uncrossed, with the right arm bared, supported, and positioned at heart level and should not have smoked, eaten, ingested caffeine or been exposed to exertion or cold for at least 30 minutes prior to the measurement. The participant should be seated and quiet for at least 5 minutes prior to the measurement, and requested not to talk while blood pressure is being taken.
- Choose appropriate cuff size for arm to be tested. The rubber bladder should encircle at least two-thirds of the arm. If the cuff is too narrow, the blood pressure reading will be erroneously high; if it is too wide, the reading may be low. A cuff that is 12-14 cm wide is satisfactory for the average adult arm.

7.6.2. Technique

- Use a standard mercury sphygmomanometer to measure the blood pressure. The mercury manometer must be handled carefully to avoid loss of mercury. The level of mercury in the tube should be observed with no pressure applied to the cuff. If necessary, mercury should be added to the reservoir to bring the edge of the mercury meniscus exactly to the zero mark. The column of the usual desk or wall manometer must be vertical for correct reading. Some mobile or floor-based mercury manometers are designed to be read at a reclined angle and the gradations are adjusted accordingly. It is important that the instrument be used with the tube and its scale in the correct position. The tube of the mercury manometer should be inspected regularly for dirt or sign of oxidation. Clogging in the air vent or filter at the top of the manometer tube will cause the mercury column to respond sluggishly to declining pressure in the bladder and will cause an erroneous reading. The filter and the vent should be serviced at least annually to ensure continued accuracy.
- Place lower edge of cuff with its tubing connections approximately 1 inch above natural crease of the inner aspect of elbow (2.5 cm above antecubital space).
- Wrap cuff snugly about arm with inflatable inner bladder centered over area of brachial artery (medial surface of arm).
- Be sure that the connecting tube attached to the mercury column is away from the participant's body and

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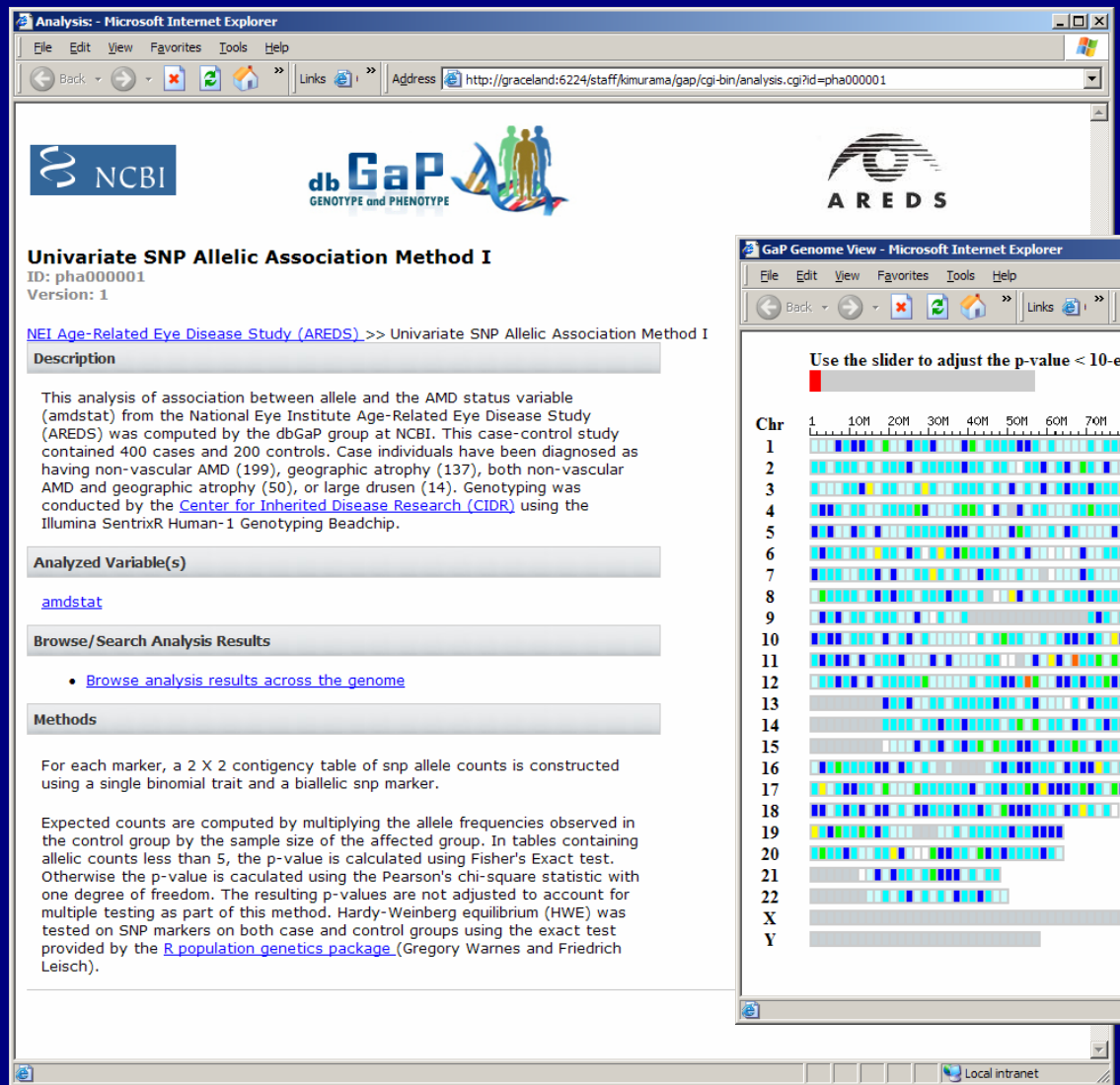
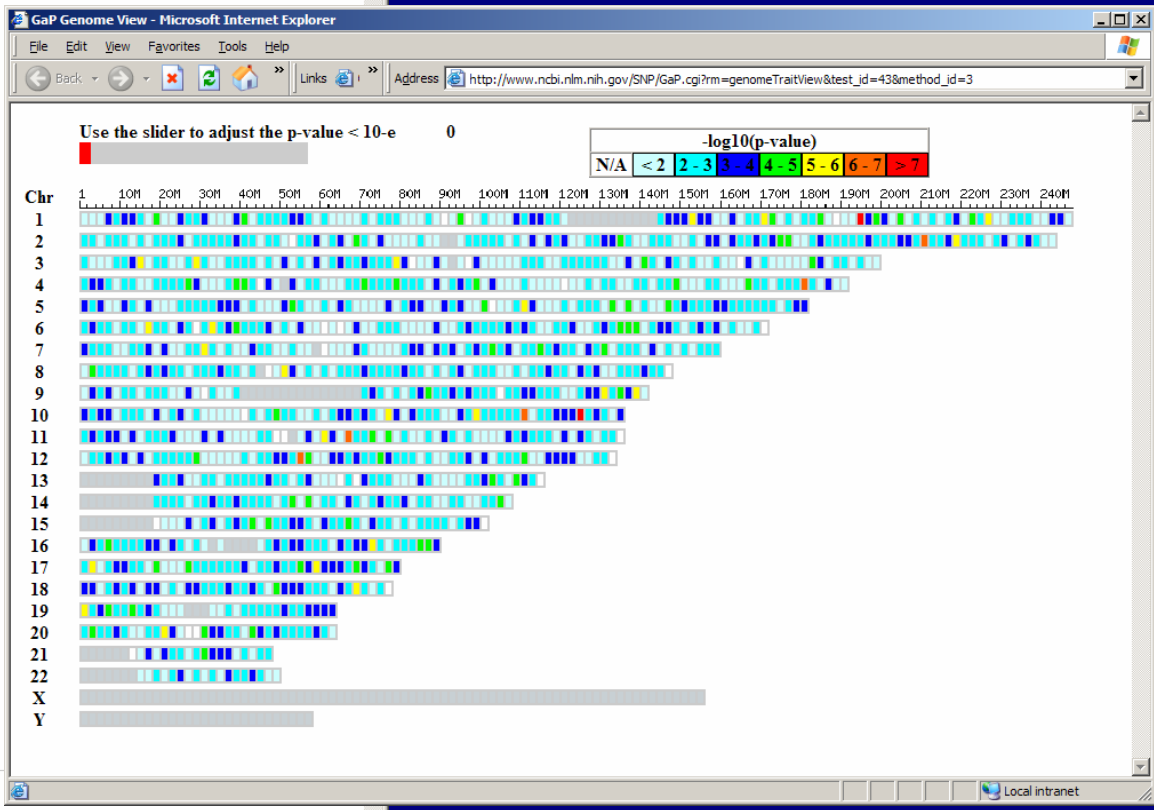
Association/Analysis Pages





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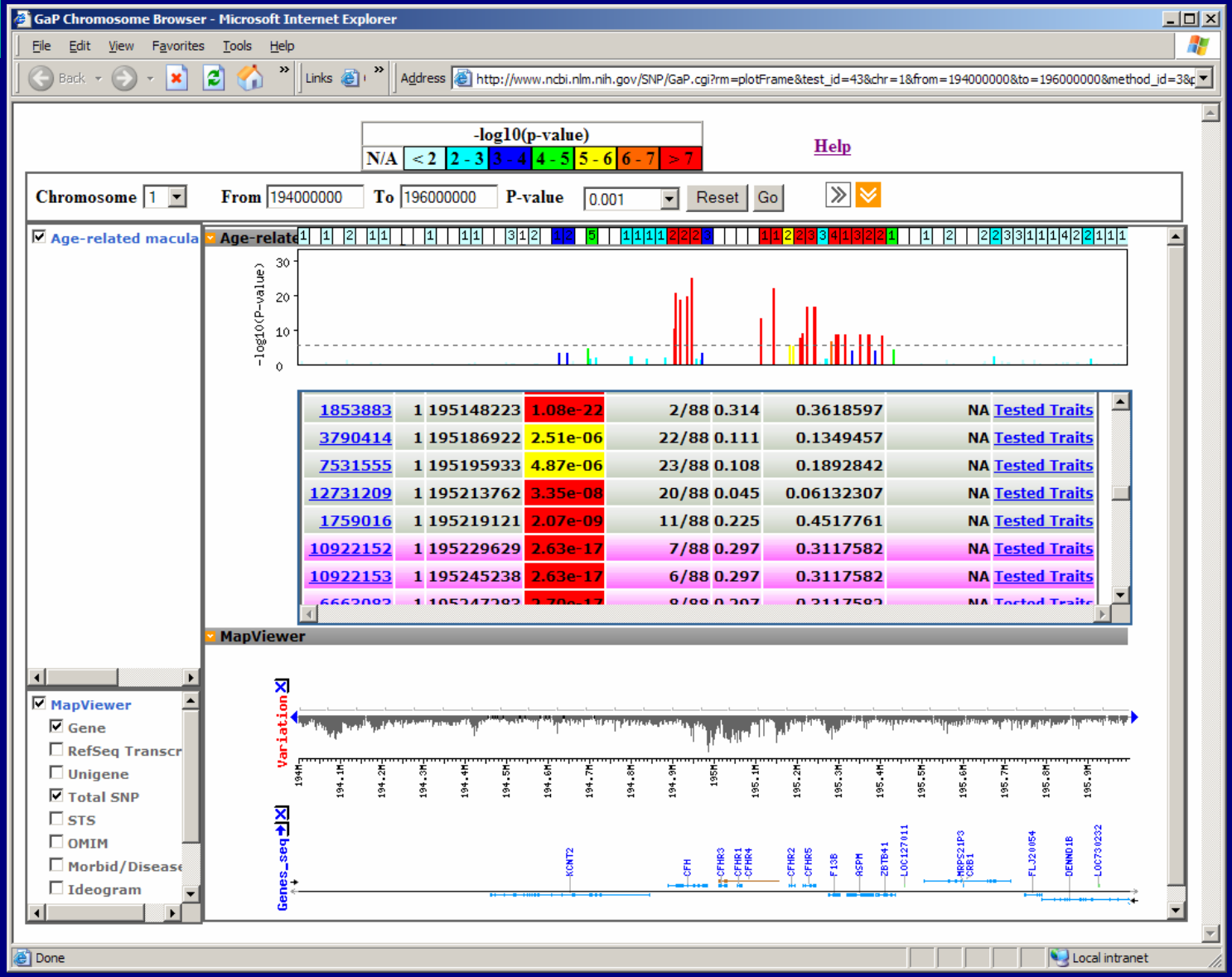
Associations Close Up



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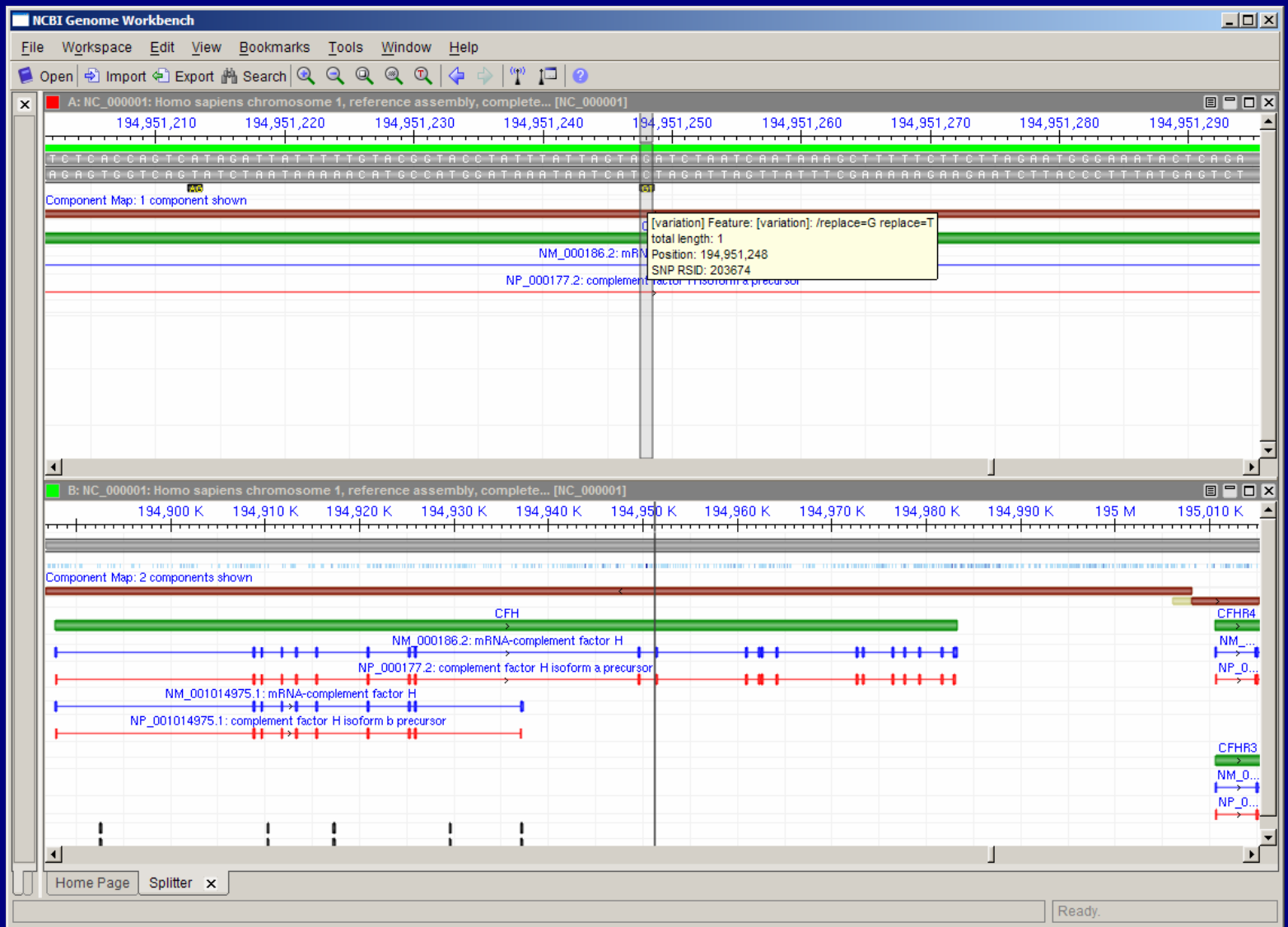
Associations to the Basepair



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Closing the Loop